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10/529,028	03/24/2005	Sarina Striem	800.1019	9002

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EXAMINER	
OH, TAYLOR V	

ART UNIT	PAPER NUMBER
1625	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/529,028	STRIEM ET AL.	
	Examiner	Art Unit	
	Taylor Victor Oh	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 June 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *32-46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *3/24/05* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Final Rejection

The Status of Claims

Claims 32-46 are pending.

Claims 32-46 are rejected.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of Claims 9 and 11-15 under 35 U.S.C. 112, first paragraph, has been withdrawn due to the cancellation of claims; however, in view of the revised claims in the amendment, Claims 32-46 are further subjected to the rejection under 35 U.S.C. 112, first paragraph, as failing to comply with the scope of enablement requirement.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 32-46 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the brain ischemia treatment, does not reasonably provide enablement for the treatment or management of a metalloproteinase-related disease or disorder recited in claim 32. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The scope of the claims is not adequately enabled solely based on the metalloproteinase inhibitor activity provided in the specification. The claims are directed to not the specific diseases, but all kinds of the diseases by using the mechanistic nature of inhibiting matrix metalloproteinase enzymes. The specification falls short because data essential for treating many diseases by means of inhibiting matrix metalloproteinase enzymes is not described in the specification.

First, the instant claims cover the treatment of diseases such as inflammatory diseases, autoimmune diseases and cancer, for which there is no enablement provided.
Enablement for the scope of "inflammation" generally is not present. For a compound or genus to be effective against inflammation generally is contrary to medical science. Inflammation is a process which can take place in virtually any

part of the body. There is a vast range of forms that it can take, causes for the problem, and biochemical pathways that mediate the inflammatory reaction. There is no common mechanism by which all, or even most, inflammations arise. Mediators include bradykinin, serotonin, C3a, C5a, histamine, assorted leukotrienes and cytokines, and many, many others. Accordingly, treatments for inflammation are normally tailored to the particular type of inflammation present, as there is no, and there can be no "magic bullet" against inflammation generally.

Inflammation is the reaction of vascularized tissue to local injury; it is the name given to the stereotyped ways tissues respond to noxious stimuli. These occur in two fundamentally different types. Acute inflammation is the response to recent or continuing injury. The principal features are dilatation and leaking of vessels, and recruitment of circulating neutrophils. Chronic inflammation or "late-phase inflammation" is a response to prolonged problems, orchestrated by T-helper lymphocytes. It may feature recruitment and activation of T- and B-lymphocytes, macrophages, eosinophils, and/or fibroblasts. The hallmark of chronic inflammation is infiltration of tissue with mononuclear inflammatory cells. Granulomas are seen in certain chronic inflammation situations. They are clusters of macrophages which have stuck tightly together, typically to wall something off. Granulomas can form with foreign bodies such as aspirated food, toxocara, silicone injections, and splinters.

Otitis media is an inflammation of the lining of the middle ear and is commonly caused by Streptococcus pneumoniae and Haemophilus influenzae. Cystitis is an inflammation of the bladder, usually caused by bacteria. Blepharitis is a

chronic inflammation of the eyelids that is caused by a staphylococcus. Dacryocystitis is inflammation of the tear sac, and usually occurs after a long-term obstruction of the nasolacrimal duct and is caused by staphylococci or streptococci. Preseptal cellulitis is inflammation of the tissues around the eye, and Orbital cellulitis is an inflammatory process involving the layer of tissue that separates the eye itself from the eyelid. These life-threatening infections usually arise from staphylococcus. Hence, these types of inflammations are treated with antibiotics. Certain types of anti-inflammatory agents, such as non-steroidal anti-inflammatory medications (Ibuprofen and naproxen) along with muscle relaxants can be used in the non-bacterial cases. The above list is by no means complete, but demonstrates the extraordinary breadth of causes, mechanisms and treatment (or lack thereof) for inflammation. It establishes that it is not reasonable to any agent to be able to treat inflammation generally.

The treatment of "autoimmune diseases" generally would be an unprecedented feat. For a compound or genus to be effective against "autoimmune diseases" generally is contrary to medical science. The "autoimmune diseases" are processes which can take place in virtually any part of the body. There is a vast range of forms that it can take, causes for the problem, and biochemical pathways that mediate the inflammatory reaction. There are dozens of such diseases, which have fundamentally different mechanisms and different underlying causes. Known autoimmune disorders include multiple sclerosis, autoimmune uveitis, rheumatoid arthritis, Addison's

disease, thyroiditis, atrophic gastritis, myasthenia gravis, idiopathic thrombocytopenic purpura, hemolytic anemia, systemic lupus erythematosus, primary biliary cirrhosis, Wegener's granulomatosis, polyarteritisnodosa, erythema nodosum leprosum, autoimmune uveitis, Guillain-Barré syndrome (GBS), allergic encephalomyelitis, acute necrotizing hemorrhagic encephalopathy, idiopathic bilateral progressive sensorineural hearing loss, aplastic anemia, pure red cell anemia, polychondritis, scleroderma, Stevens-Johnson syndrome, idiopathic sprue, lichen planus, Crohn's disease, Graves ophthalmopathy, sarcoidosis, primary biliary cirrhosis, type I diabetes, autoimmune optic neuritis, uveitis posterior, or interstitial lung fibrosis, alopecia, Sjogren's Syndrome, Goodpasture Syndrome, Myasthenia Gravis, inflammatory bowel disease and many more.

There are both chronic and acute "autoimmune diseases", most of which lack satisfactory treatment. The intractability of these disorders is clear evidence that the skill level in this art is low relative to the difficulty of the task. Under such circumstances, it is proper for the PTO to require evidence that such an unprecedented feat has actually been accomplished. The failure of skilled scientists to achieve a goal is substantial evidence that achieving such a goal is beyond the skill of practitioners in that art, *Genentech vs. Novo Nordisk*, 42 USPQ2nd 1001, 1006.

Since no compound has shown clinical efficacy against all autoimmune diseases, thus no *in vivo* or *in vitro* assay could be validated for the identification

of such a general agent. Applicants' specification logically must lack such assay data.

In fact, there are four basic mechanisms underlying autoimmune disease: 1. Antibody mediated diseases: a specific antibody exists targeted against a particular antigen (protein), which leads to its destruction and signs of the disease. Examples are: auto-immune mediated hemolytic anemia, where the target is on the surface of the red blood cell; myasthenia gravis where the target is the acetylcholine receptor in the neuromuscular junction; hypoadrenocorticism (Addison's) where the targets are the cells of the adrenal gland. 2. Immune-complex-mediated diseases: antibodies are produced against proteins in the body. These combine into large molecules that circulate around the body. In systemic lupus erythematosus (SLE) antibodies are formed against several components in the cell's nucleus (hence the anti-nuclear antibody test (ANA) for SLE). Most notably antibodies are made against the body's double stranded DNA, and form circulating soluble complexes of DNA and antibody, which break down in skin causing an increased sensitivity to ultraviolet light and a variety of signs. As the blood is filtered through the kidneys, the complexes are trapped in the glomeruli and blood vessels, causing the kidney to leak protein - glomerulonephritis. They also cause leakage in other blood vessels, and there may be hemorrhaging, as well as accumulating in synovial fluid and causing signs of arthritis and joint pain. Rheumatoid arthritis results from immune complexes (IgM class antibody called rheumatoid factor) against part of the patient's own immune system (part of its IgG molecules). These form complexes

that are deposited in the synovia of the joint spaces causing an inflammatory response, joint swelling, and pain. The collagen and cartilage of the joint breaks down and is eventually replaced by fibrin which fuses the joints - ankylosis. 3. Antibody and T Cell-mediated diseases: T cells are one of two types (the other being B-cells), which mediate immune reactions. Upon exposure to a particular antigen, they become programmed to search for and destroy that particular protein in future. Once a patient has been exposed to an antigen, he will be able to mount a much faster response to it the next time it encounters it. This is the basis of vaccination. Thyroiditis (autoimmune hypothyroidism) seems to be of mixed etiology. Several target antigens have been identified, including thyroglobulin the major hormone made by the thyroid. Auto-antibodies to antigens in the epithelial cells of the thyroid have also been found. The thyroid becomes invaded by large numbers of T and B cells as well as macrophages, which are cells that engulf and destroy other cell types. T cells specifically programmed for thyroglobulin have been identified. 4. Diseases arising from a deficiency in complement: When an antigen and antibody react they may activate a series of serum enzymes (the complement system) whose end result is either the lysis (breakup) of the antigen molecule or to make it easier for phagocytic cells like the macrophages to destroy it. Patients with deficiencies in enzymes activated early in the complement system develop autoimmune diseases like SLE.

Thus, with such differing mechanisms, it is not logical that a treatment for autoimmune diseases generally can be found.

The claim sets forth the treatment of cancer generally. However, there never has been a compound capable of treating cancer generally. There are compounds that treat a range of cancers, but no one has ever been able to figure out how to get a compound to be effective against tumors generally, or even a majority of tumors. Thus, the existence of such a "silver bullet" is contrary to our present understanding in oncology. Even the most broadly effective antitumor agents are only effective against a small fraction of the vast number of different cancers known. This is true in part because cancers arise from a wide variety of sources, such as viruses (e.g. EBV, HHV-8, and HTLV-1), exposure to chemicals such as tobacco tars, genetic disorders, ionizing radiation, and a wide variety of failures of the body's cell growth regulatory mechanisms. Different types of cancers affect different organs and have different methods of growth and harm to the body, and different vulnerabilities. Thus, it is beyond the skill of oncologists today to get an agent to be effective against cancers generally, evidence that the level of skill in this art is low relative to the difficulty of such a task.

Further, "tumor" covers more than just cancers. It also covers many neoplasms, cancerous or not. A neoplasm is any abnormal tissue that grows by cellular proliferation more rapidly than normal, or continues to grow after the stimulus that initiated the new growth has ceased, or shows lack (partial or complete) of structural organization and/or coordination with surrounding tissue. It can be benign or malignant. Thus, such a term, also covers precancerous conditions such as lumps, lesions, and polyps.

In addition, "tumor" covers things other than neoplasms. It also covers any kind of swelling arising from inflammation. Thus, the claim would cover treatment of many kinds of inflammation. The specification cannot support that.

When the best efforts have failed to achieve a goal, it is reasonable for the PTO to require evidence that such a goal has been accomplished, *In re Ferens*, 163 USPQ 609. The failure of skilled scientists to achieve a goal is substantial evidence that achieving such a goal is beyond the skill of practitioners in that art, *Genentech vs Novo Nordisk*, 42 USPQ2nd 1001, 1006.

In evaluating the enablement in question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

The Nature of the Invention

The nature of the invention in claims 32-37 , and 40-44 is a method for treating or managing a metalloproteinase(MMP)- related disease or disorder in a mammal comprising administering to the mammal in need a pharmaceutical composition containing a compound of the formula (I).

The State of the Prior Art

The state of the prior art is that according to US Patent No. 5,948,780, MMP inhibitors have been used to prevent and treat congestive heart failure and

other cardiovascular diseases. Recent data has revealed that specific enzymes are closely related to some diseases ,while there is no effect on other diseases. The MMPs are generally classified based on their substrate specificity; particularly , the collagenase subfamily of MMP-1, MMP-8, and MMP-13 selectively cleave interstitial collagen tissue. This has been noticed by the discovery that only MMP-13 is over expressed in breast carcinoma, whereas MMP-1 alone is over expressed in papillary carcinoma (see Chen et al., J. Am .Chem. Soc., 2000;122;9648-9654). Furthermore, according to Wo/01/63244A1 and US Patent No. 6,008,243 few selective inhibitors of MMP-13 have been approved.

> Stable lipophilic diesters of the divalent metal ion chelator 1,2-bis(2 aminophenoxy)ethane-N,N,N',N'-tetraacetic acid (BAPTA) have been disclosed in the International Patent Publication No. WO 99/16741 of the same applicant. Also disclosed in this publication is the use of these compounds in pharmaceutical compositions useful for treating diseases and disorders related to excess of divalent metal ions. Among these diseases and disorders are ischemia, stroke, epilepsy and neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease.

; however, no selective or nonselective inhibitor of MMP-9 has been approved for treating any disease in any animal.

The predictability or lack thereof in the art

The instant claimed invention is highly unpredictable as discussed below:

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. In re

Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the instant claimed invention is highly unpredictable since one skilled in the art would recognize that inhibiting the MMPs would result in only the specific sites of the interstitial collagen tissue; this kind of treatment can not translated to all the possible treatment of any disease in regards to their therapeutic effects.

Hence, in the absence of a showing of correlation between all the diseases claimed as capable of treatment by the compounds of formula I and the inhibition of matrix metalloproteinase, one of skill in the art is unable to fully predict possible results from the administration of the claimed compounds of formula I due to the unpredictability of the role of inhibiting the MMPs, i.e. whether promotion or inhibition would be beneficial for the treatment of the diseases.

The nature of pharmaceutical arts is that it involves screening *in vitro* and *in vivo* to determine which compounds exhibit the desired pharmacological activities. There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face.

The amount of direction or guidance present

The direction present in the instant specification is that the compounds of formula I can inhibit the MMPs which helps in the treatment for various diseases

listed on page 8. However, the specification is silent and fails to provide guidance as to whether the diseases listed (page 8) require the inhibition of the MMPs for treatment, i.e. the specification fails to provide a correlation between the diseases listed and the inhibition of the MMPs. Also, there is no direction and guidance for the inhibition of the MMPs for the treatment of any kinds of diseases.

The presence or absence of working examples

There are some conclusive statements for ameliorating disease and conditions related to peripheral inflammatory processes, usefulness in interfering with damaging neuron-inflammatory processes, and the neuron-protective effect for the brain ischemia in vivo test. Furthermore, there are not other working examples for any other diseases listed in the specification. Also, the compounds which are discloses in the specification have no pharmacological data regarding the treatment of any other disease besides inhibitory activity of various MMPs using compounds from various classes and have no data on the possible treatment of the various diseases that require the inhibitory activity of various MMPs. Also, the specification fails to provide sufficient working examples as to how the listed diseases can be treated by the inhibition of various MMPs, i.e. again, there is no correlation between the diseases listed and inhibition of various MMPs.

The breadth of the claims

The breadth of the claims is that the compounds of formula I can treat any disease by the inhibition of the MMPs , without regards as to the affect of the inhibition of the MMPs on the stated diseases.

The quantity of experimentation needed

The quantity of experimentation needed is undue experimentation. One of skill in the art would need to determine what listed diseases would be benefited by the inhibition of the MMPs and would furthermore then have to determine whether the claimed compounds would provide treatment of the disease by the inhibition of the MMPs.

The level of the skill in the art

The level of skill in the art is high. However, due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by in vitro and in vivo screening to determine which compounds exhibit the desired pharmacological activity and which diseases would benefit from this activity.

Thus, the specification fails to provide sufficient support of the broad use of the compounds of formula I for the treatment of any disease by the inhibition of the MMPs. As a result, necessitating one of skill to perform an exhaustive search for which diseases can be treated by the compounds of formula I in order to practice the claimed invention.

Genentech Inc. v. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001 , states that " a patent is not a hunting license. It is not a reward for search , but

compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the Wands factors and In re Fisher (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in undue experimentation to test which diseases can be treated by the compound encompassed in the instant claims, with no assurance of success.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The rejection of Claims 9 and 11-15 under 35 U.S.C. 112, second paragraph has been withdrawn due to the cancellation of the claims.

Claim Rejections - 35 USC § 102

The rejection of Claims 9, 11,13, and 15 under 35 U.S.C. 102(b) as being anticipated clearly by Kozak et al (WO99/16741) has been withdrawn.

However, in view of the revised claims in the amendment, the following office action has been issued.

Claim Rejections - 35 USC § 103

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

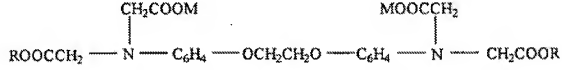
> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 32-39,44-46 rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Kozak et al (WO99/16741).

Kozak et al discloses the followings(see page 9 ,lines 15-26):



Formula 1

wherein the substituents on the aromatic rings are in the ortho position;
R is selected from the group consisting of C_nH_{2n+1} (n=1-10), $C_nH_{2n+1}(OCH_2CH_2)_m$ (n=1-20, m=1-6), $(C_nH_{2n+1})_2N(CH_2)_m$ (n=1-6, m=1-6) and substituted or unsubstituted $ArCH_2$; and M denotes any physiologically acceptable cation.

> The compounds of the invention may be useful in open heart surgery and for the treatment of medical conditions associated with increased levels of divalent metal ions, in particular calcium. These conditions may include, but are not limited to, brain and cardiac ischemia, stroke, myocardial infarction, epilepsy, chronic neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and acute inflammation as well as diseases associated with neuronal and muscular hyperactivity such as urinary incontinence, prostatic hypertrophy, muscular spasm, arterial hypertension, asthma and irritable bowel syndrome.

(see page 12 ,lines 3-10).

However, the instant invention differs from the prior art in that MMP-related diseases or disorders are unspecified.

Even so, many diseases such as brain and cardiac ischemia, neuronal and muscular hyperactivity diseases can be treated irrespective of never mentioning the use of the mechanistic nature of inhibiting matrix metalloproteinase enzymes for the treatment in the prior art. Furthermore, it is a well known fact that a similar chemical structure in the compounds gives rise to expectation of similar chemical properties. ***In re Gyurik***, 201 USPQ 552(CCPA 1979) and ***In re May*** , 197 USPQ 601(CCPA 1978). Moreover, they are identical with each other with respect to their corresponding chemical formula. Therefore, it would have been obvious to the skilled artisan in the art to be motivated to research and discover the role of the mechanistic nature of inhibiting effect of the prior art compound on the matrix metalloproteinase enzyme in an alternative pursuit for treating those claimed diseases by a routine experimentation.

Applicants' Argument

Applicants' argument filed 6/19/08 have been fully considered but are not persuasive.

Applicants argue the following issues:

a. The currently claimed method of treating MMP-related conditions is completely different and wholly unexpected from the elevated divalent metal ion treatment described in the prior art;

b. Dependent claims 35-37, and 41-44 list only MMP-related conditions which do not overlap with those conditions related to divalent metal ion elevation in the prior art.

Applicants' arguments have been noted, but the arguments are not persuasive.

First, regarding the first and second arguments , the Examiner has noted applicants' arguments. However, as indicated in the above, regardless of lacking in mentioning the mechanistic nature of inhibiting matrix metalloproteinase enzymes other than the elevated divalent metal ion the treatment in the prior art, the end result is still the same treatment for the same diseases of the claimed invention as described in the prior art (see page 12 ,lines 3-10). Moreover, they are identical with each other concerning their corresponding chemical formula.

Therefore, it would have been obvious to the skilled artisan in the art to be motivated to research and discover the role of the mechanistic nature of inhibiting effect of the prior art compound on the matrix metalloproteinase enzyme in an alternative pursuit for treating those claimed diseases by a routine experimentation.

Therefore, applicants' argument is not persuasive.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will

the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Taylor Victor Oh whose telephone number is 571-272-0689. The examiner can normally be reached on 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on 571-272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Taylor Victor Oh/
Primary Examiner, Art Unit 1625

9/26/08